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| 09/394,867 | 09/13/1999 | DAVID A. WILLIAMS | 7037-377/IU- | 5039 |

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| EXAMINER | |
|---|---|
| NGUYEN, DAVE TRONG | |
| ART UNIT | PAPER NUMBER |
| 1633 | 12 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/394,867 | WILLIAMS, DAVID A. | |
| | Examiner | Art Unit | |
| | Dave Nguyen | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-93* is/are pending in the application.

4a) Of the above claim(s) *70-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-69 and 79-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The specification has been amended, and claims 24, 32, 44, 52, 62 and 84 have been amended by the amendment filed September 20, 2001.

Claims 70-78 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Elected claims 11-69 and 79-93, to which the following grounds of rejection remainapplicable, are pending.

Claims 52 and 62 are objected under Sequence Rules 1.821 because the claims do not conform to the requirements of 37 CFR 1.821 because these claims recite a specific residue number for which there is no indicated SEQ ID NO:__ identifier in the claims. The requirement for compliance in 37 CFR 1.821(c) is directed to "*disclosures* of nucleotide and/or amino acid sequences." (Emphasis added.) All sequence information, whether claimed or not, that meets the length thresholds in 37 CFR 1.821(a) is subject to the rules. Furthermore, Sequence rules 37 CFR 1.821(d) requires the use of SEQ ID No: even if the sequence is embedded in the text of the description or in the claims. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Appropriate correction is required.

Claim 90 is objected because it appears that the claim contains a typographical error. The claim recites "The method of claim 89", however, claim 89 recites "The cellular population". Claim 90 should recites "The cellular population of claim 89". Clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, 33, 36-47, 51-55, 57-66, 68, 69, 82, 85, 89 and 92 readable on a genus of amino acid sequences sufficiently similar to SEQ ID NO: 1 or SEQ ID NO: 2, and of amino acid sequences that must exhibit a binding activity as claimed, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification and the state of the prior art only describe and provide sufficient description of SEQ ID NOS 1 and 2, functionally active fibronectin and fibronectin fragments that retain the claimed biological function, *e.g.,* the binding activity of the CS-1 domain of fibronectin ad of the heparin-II binding domain of fibronectin.

Applicant's disclosure of one species of functionally active fibronectin does not provide sufficient description of the specific structures of a representative number of unspecified protein sequences other than functionally active fibronectin peptides that would support applicant's possession of the genus of amino acid sequences which must possess the claimed biological activities. In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims, *e.g.* genus of similar amino acid sequences and/or unspecified amino acid sequences with the required properties as recited in the claim, requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays identifying the "agents"; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of therapeutic nucleic acid reagents.

It is not sufficient to support the present claimed invention by disclosing simply functionally active fibronectin because disclosure of no more than that, as in the instant case, is simply a wish to know the

identity of any and/or all other amino acid sequences as contemplated by the specification and the claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming all amino acid sequences that must possess the biological property as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of "amino acid sequences" and/or "similar amino acid sequences" as claimed, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's response (pages 6 and 7 of the response filed September 20, 2001) has been considered by the examiner but is not found persuasive for the reasons set forth in the stated rejection and for the following reasons:

In response to applicant's assertion (the response, pages 6 through 7) that the disclosure is sufficiently described so as to enable one skilled artisan to practice the full breadth of the invention as intended, and that biotechnology art is routine with respect to the use of mutation and/or deletion assays to determine a variant of a known polypeptide and yet retaining the biological function of the know polypeptide, is sufficient to reasonably convey to a skilled artisan that applicants had possession of the genus claim of the polypeptide, applicant's response is not found persuasive because of the reasons set

forth in the stated rejection, and because applicant's inference to the variants derived from a known polypeptide (firbronectin) being claimed is not reflected in the pending claims. The breadth of the claims embraces a genus of number of unspecified polypeptide sequences other than a functionally active fibronectin and yet the as-filed specification does not provide a sufficient description of a representative number of species of the claimed genus. The issue is not that the claims have to be restricted to a specifically named SEQ ID NO. encoding a fibronectin protein or fragment, nor is it that undue experimentation is lacking to discover functionally active fibronectin fragments other than the SEQ ID NO. 1 disclosed by the specification, but rather the issue is the lack of sufficient description of the genus of unspecified amino acid sequences as claimed. Note also that applicant's assertion at best is simply an opinion and consclusory and does not provide any factual evidence to overcome the outstanding reasons and issues set forth properly in the stated rejection under 35 USC 112, first paragraph.

Claims 32, 33, 36-47, 51-55, 57-66, 68, 69, 82, 85, 89 and 92 readable on a genus of amino acid sequences sufficiently similar to SEQ ID NO: 1 or SEQ ID NO: 2, and of amino acid sequences that must exhibit the binding activities as claimed are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to fibronectin or fibronectin fragments that exhibit the binding activities as claimed.

The specification does not reasonably provide enablement for the presently pending claims encompassing any and/or all immobilized materials containing unspecified ligands, and any and/or all "similar amino acid sequences" as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance

presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically and with respect to the claims, since the claimed invention is not supported by a sufficient written description, particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended.

In addition, the application does not provide sufficient guidance and/or factual evidence to enable one skilled in the art to practice the invention directed to a method for increasing the frequency of transduction of all viable mammalian cells by a replication-defective retrovirus vector by using an effective immobilized amount of material other than active fibronectin fragments which encode Heparin II binding domains, nor is it apparent how one skilled in the art reasonably extrapolates from the disclosure including the exemplified *in vitro* data to the transduction methods as claimed, wherein an increase of retroviral transductions is affected by the presence of an unspecified materials, ligands, and/or polypeptides. Furthermore, it is not apparent how one skilled in the art determines without undue experimentation on the basis of applicant's disclosure as to which polypeptides other than active fibronectin polypeptides, *e.g.*, Heparin II binding domain and VLA-4 binding domain of fibronectin, increase the transduction of a retroviral vector into any viable mammalian cells including human pluripotent stem cells. Note also that Moritz *et al.* (J. Clin. Invest, 1994) teach that the underlying biochemical and molecular mechanism of fibronectin which affects the transduction efficiency of retroviral vectors into hematopoietic stem cells is not known. In addition, the application and claims contemplate that amino acid sequences similar to SEQ ID NO: 1 (encoding a Heparin II binding domain of fibronectin) and any amino acid sequence derived or obtained from collagen or fibroblast growth factors are also effective to increase transduction of retroviral vectors into any target cell. However, it is not apparent as to how one skilled in the art identifies and/or determines, without any undue experimentation, as to which "similar amino acid sequences" is effective for binding to a retroviral vector and affects a transduction efficiency of a retroviral viral vector into any viable mammalian cell. The problem of predicting protein structure from mere sequence data of a single

amino acid or nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of any nucleic acid sequence and finally what changes can be tolerated with respect thereto is complex and do not invariably follow empirical rules. Unpredictability is keyed on the fact that simple analysis of primary, secondary, tertiary, and quaternary structure of a polypeptide is not well correlated with the ability of the encoded DNA product to its functional activity because the relationship between the amino acid sequence of a polypeptide and its tertiary and/or quaternary structure is not well understood and is not invariably predictable (see Ngo *et al.,* in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.,* (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). Thus, one skilled in the art would have to exercise an undue experimentation to employ any polypeptides or ligands other than fibronectin for the purpose of enhancing retrovirus transduction in the a cell culture of viable hematopoietic stem cells.

For the reasons discussed above, it requires undue experimentation to practice the full scope of claimed invention as claimed, particularly given the breadth of the claims, the amount of undue experimentation necessary because of the absence of guidance and the lack of reasonable correlation between the data obtained from the working examples to the subject matter being sought in the claims, and the unpredictable nature of the art.

In response to applicant's assertion (pages 8 and 9 of the response) that sufficient guidance was provided by the specification to enable a skilled artisan to practice the full breadth of the claims, and that it is routine in the art to go to existing sequence databases to utilize sequences sufficiently similar to the disclosed SEQ ID NO: for the practice of the claimed invention, the comments are not persuasive because of the reasons set forth in the stated rejection, and because the issue is not that the stated rejection attempts to restrict applicant's invention to just the disclosed SEQ ID NO encoding a fibronectin. The issue is the breadth of the "substantially similar sequences" which does not reasonably convey to a skilled artisan as to what is exactly applicant's intended scope of the claims, nor does it reasonably convey to a skilled artisan as to how to utilize substantially similar sequences that are yet to be discovered at the time the invention was made, wherein such sequences are not necessarily functionally fibronectin

fragments. Applicant's argument as to existing database providing the full breadth of the claims is simply consclusory and expresses an opinion and thereby is not found persuasive. Note also that it is the as-filed specification that must provide the essential materials which include sequences other than functionally active fibronectin fragments and yet has the same activity as a fibronectin protein for the practice of the full scope of the invention.

Claims 24, 25, 32-37, 42, 44-56, 62-66 and 84-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is only enabling for:

1/ An improved method of cellular grafting, comprising the steps of:

obtaining viable hematopoietic cells from a murine donor;

infecting the viable hematopoietic cells with a replication-defective recombinant retrovirus vector containing exogenous DNA to produce transduced viable hematopoietic cells, the infecting being in the presence of an immobilized amount of fibronectin and/or a fragment thereof effective to increase the efficiency of cellular transduction by the retrovirus vector; and

introducing the transduced viable hematopoietic cells into said murine donor as a cellular graft; does not reasonably provide enablement for any other claimed embodiment wherein a therapeutically relevant effect as a result of the grafting is contemplated; and

2/ A method for increasing the frequency of transduction of hematopoietic cells *in vitro* by a retrovirus vector, comprising

infecting the viable hematopoietic cells with a replication-defective recombinant retrovirus vector containing exogenous DNA to produce transduced viable hematopoietic cells, the infecting being in the presence of an immobilized amount of fibronectin and/or a fragment thereof effective to increase the efficiency of cellular transduction by the retrovirus vector.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification demonstrates the increased frequency of transduction of NIH/ 3T3 and

clonogenic bone marrow cells using a medium containing active fibronectin fragments (active for binding to both target cells and retrovirus vectors, Example 15). Examples 1-11, and 13-14 demonstrates the efficiency of transduction of various types of viable cells, *e.g.,* hematopoietic stem cells, c-KIT+ cells, BFU-E cells, progenitor cells, and cord blood cells, by a replication-defective retrovirus in a medium containing fibronectin fragments and polybrene.

Since the application indicates that "the invention provides a method of somatic gene therapy which involves *in vitro* cellular therapy and subsequent transplantation of target cells into a host, also known as "engraftment" of the host with the transduced target cells. Thus, the only intended use of the cellular grafting methods in the absence of the stated positive effect cited in the claims is to have a therapeutically relevant effect in any and/or all animals. However, the specification fails to disclose as to what are the metes and bounds of a stated positive effect resulted from *in vivo* cellular grafting methods as claimed. No details are given for administration of the cells, such as numbers of cells needed for a particular injury or disease, or the route of administration for each application. The specification fails to provide guidance to the artisan on these essential aspects of the invention. When treating different types of injury using the grafting methods, can the cells be infused intravenously and be expected to have sufficient gene expression to correct a defect at any target site? Are the dosage of transduced viable cells, pluripotent stem cells, for *e.g.* treatment of protein deficiency different from treatment for improving resistance to chemotherapy? What number of cells is sufficient? The answer to each of these questions is essential to the successful use of the invention, however the specification gives no guidance as to the essential factors so as to enable one skilled in the art to practice the full scope of the claimed invention as claimed. Furthermore, the state of the art exemplified by Moritz *et al.* indicates that *ex vivo* gene therapy using genetically modified cell for engraftment into any an animals remain unpredictable. Note the Moritz *et al.* reference (J. Clin. Invest. 1994, 93:1451-1457) indicating that "although gene transfer and long term gene expression in repopulating stem cells have been achieved in murine models by a number of investigators, *in vivo* experiments in larger animals such as dogs and primates have met with limited success, largely because of the low efficiency of infection of primitive hematopoietic stem cells". Thus, in

absence of any *in vivo* data regarding the grafting methods in any and/or all animals other than a murine model, it is not apparent how one skilled in the art determines the appropriate combination of transfection method, level of expression, cell numbers and method of administration for each possible gene, so as to have a therapeutic effect in any and/or all animals, without undue experimentation.

More specifically as to the state of the art of *ex vivo* gene therapy of employing any genetically modified hematopoietic cell expressing a transgene coding for an enzyme, *e.g.,* adenosine deaminase, Onodera *et al.,* Acta Haematologica, 101, 2, pp. 89-96, 1999, indicates that even in 1999, the retroviral-mediated gene transfer to hematopoietic stems was insufficient for achievement of any therapeutically relevant effect (abstract). Kohn , Current Opinion in Pedatrics, 7, 56-63, 1995, indicates that the efficiency of gene transfer into stem cells was much lower when similar protocols were assessed in large mammals and in human gene therapy trials, suggesting that there are species-specific differences in the susceptibility of stem cells to retrovirus infection" (p. 58, column 1). Kohn further teaches that effective gene therapy for hematologic disorders remains unpredictable, and that a detection of circulating vector sequences in the blood *in vivo* after a transplantation of hematopoietic stem cells containing gene therapy vectors is not equivalent to a therapeutic effect (page 59, columns 1 and 2). There are no working examples in the specification which indicates the efficiency of transduction in pluripotent HSCs of any mammal including humans wherein a therapeutic effect is generated. With respect to a type of stem cells used in the claimed method, one skilled in the art would require its isolation, and the establishment of its long term stem cells. In view of the difficulty of isolating the entire range of stem cells, such as sweat gland, mucous stem cells, and human pluripotent hematopoietic stem cells, and further in the absence of any guidance with respect to a produced therapeutic effect due a number of obstacles in view of the reasons set forth in the stated rejection, it would require undue experimentation for one skilled in the art to practice the claimed invention as claimed without undue experimentation, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record. More specifically as to claims encompassing gene therapy methods of employing autologous, allogeneic and xenogeneic transplantation of nearly any genetically modified cell from any mammal to any other mammal to have a therapeutic

effect, transplanted cells from any subject to any other subject may not be truly syngeneic with their host mammal. Any such transplantation into immunocompetent hosts would result in a strong rejection response which would ultimately destroy the host. Thus, the specification gives no guidance as to how to control such immune responses in any mammal if such transplantation is employed in the claimed methods, nor is it apparent what diseases or disorder are effected by the transplanted cells expressing a therapeutic gene. In fact, the state of the art exemplified by Riddell *et al.* (Nature Medicine, Vol. 2, 2:216-223, 1996) indicates that one unexpected insight from *ex vivo* gene therapy against HIV infected cells in a immuno-competent host was the ability of HIV-infected patients to induce strong primary T-cell immune responses to foreign antigens expressed by transferred autologous cytotoxic CD8+ T cells (p. 221, column 1), and that the rejection of genetically modified cells by immunocompromised hosts suggests that strategies to render gene-modified cells less susceptible to host immune surveillance will be required for successful gene therapy of immuno-competent hosts (abstract, page 221, column 1).

Even if some of the genetically modified immune cells escape from the immune response in a survived host after systemic administration, it is further not apparent to one skilled in the art as to how the genetically modified immune cells traverse though barriers such as peripheral vein and endothelial wall to reach target diseased cells, *e.g.,* cancerous, virally infected cells, so as to generate any and/or all therapeutic effects as contemplated by applicants. Thus, it is not apparent how the murine model wherein hematopoietic stems expressing ADA were grafted as evidenced in the prior art at the time the invention was made is reasonably extrapolated to any therapeutically relevant effects generated in any and/or all diseased animals other than mice by using the claimed materials and/or method steps, particularly in view of the reasons set forth above. Note that while the improvement claims indicates an improvement of existing cellular grafting methods of employing genetically modified hematopoietic stem cells in any and/or animal, cellular grafting methods of employing genetically modified hematopoietic stem cells in any and/or animal that exists in the prior art of record and the improvement method as claimed so as to have a therapeutic effect still remain unpredictable at the time the invention was made, particularly given the reasons set forth above and the doubts expressed in the art of record.

In view of the lack of guidance regarding the breadth of the claims, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the full scope of the invention as claimed.

Applicant's response (pages 8 and 9) have been considered by the examiner but is not found persuasive for the reasons set forth in the stated rejection and for the following reasons

Applicant argued on page 8 that since guidance and teachings has been provided by the specification with respect to the diseases including ADA deficiency, pediatric acute myelogenous leukemia, neroblastoma, and that the routes of administration, the dosage of cells, level of expression are known in the art using routine procedure. However, the issue is not that applicants did not provide a specific, substantial and credible utility for the cellular grafting method within the context of therapeutic applications of the above diseases. The issue is whether or not on the basis of applicant's disclosure, the state of the prior art, the knowledge of a skilled artisan, the working examples, the breadth of the claims, the nature of the invention, an undue experimentation is required to practice the therapeutic applications by using genetically modified hematopoietic stem cells as contemplated by the as-filed specification. The answer as stated in the stated rejection is that while the improvement claims indicates an improvement of existing cellular grafting methods of employing genetically modified hematopoietic stem cells in any and/or animal, cellular grafting methods of employing genetically modified hematopoietic stem cells in any and/or animal that exists in the prior art of record and the improvement method as claimed so as to have a therapeutic effect still remain unpredictable at the time the invention was made, particularly given the reasons set forth above and the doubts expressed in the art of record.

Applicants further argued that since Moritz indicates that "although gene transfer and long term gene expression in repopulating stem cells have been achieved in murine models by a number of investigators, *in vivo* experiments in larger animals such as dogs and primates have met with limited success, largely because of the low efficiency of infection of primitive hematopoietic stem cells", the "limited success" is more than enough for patenting purposes. Applicants appear to imply that "limited success" of *"in vivo experiments"* in larger animals is equated to the "limited success" of therapeutic

applications of any genetically modified hematopoeitic cells. However, the Moritz coupled with the totality of the prior art as a whole does not support applicant's assertion. A simple and limited, transient expression of a transgene in hematopoeitic stem cells *in vivo* is not the same as a therapeutically relevant effect as a result of such *in vivo* gene expression. In fact and more specifically as to the state of the art of *ex vivo* gene therapy of employing any genetically modified hematopoietic cell expressing a transgene coding for an enzyme, *e.g.,* adenosine deaminase, Onodera *et al.,* Acta Haematologica, 101, 2, pp. 89-96, 1999, indicates that even in 1999, the retroviral-mediated gene transfer to hematopoietic stems was insufficient for achievement of any therapeutically relevant effect (abstract). Kohn , Current Opinion in Pediatrics, 7, 56-63, 1995, indicates that the efficiency of gene transfer into stem cells was much lower when similar protocols were assessed in large mammals and in human gene therapy trials, suggesting that there are species-specific differences in the susceptibility of stem cells to retrovirus infection" (p. 58, column 1). Kohn further teaches that effective gene therapy for hematologic disorders remains unpredictable, and that a detection of circulating vector sequences in the blood *in vivo* after a transplantation of hematopoietic stem cells containing gene therapy vectors is not equivalent to a therapeutic effect (page 59, columns 1 and 2). Riddell *et al.* (Nature Medicine, Vol. 2, 2:216-223, 1996) indicates that one unexpected insight from *ex vivo* gene therapy against HIV infected cells in a immuno-competent host was the ability of HIV-infected patients to induce strong primary T-cell immune responses to foreign antigens expressed by transferred autologous cytotoxic CD8+ T cells (p. 221, column 1), and that the rejection of genetically modified cells by immunocompromised hosts suggests that strategies to render gene-modified cells less susceptible to host immune surveillance will be required for successful gene therapy of immuno-competent hosts (abstract, page 221, column 1). Thus on the contrary of applicant's opinion and assertion, the state of the art with respect to therapeutic applications of genetically modified hematopoietic stem cells from any source to treat any diseased mammal remains unpredictable at the time the invention was made. The specification at the time the invention was made fails to provide sufficient guidance as to how overcome the problems and doubts expressed by the art of record. As a result, the stated rejection is proper and does provide objective evidences as to the lack of reaosnable

enablement from the as-filed specification with respect to the therapeutic applications of any genetically modified hematopoietic stem cells from any source to treat any diseased mammal.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 33, 37, 41, 49, 52, 55, 57, 60 62, 65, 82, 85, 89 and 92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37, 52, 57, 62, 82, 85, 89 and 92 are indefinite in the recitation of "sufficiently similar" because the term is relative in meanings and does not contain a reference point for determining applicant's intended scope of the claims.

Applicants argued on page 9 that one skilled artisan would know the scope of the claim by reviewing the entire claim, and that routine procedures are available to determine the "substantially similar". Applicant's argument is again consclusory and appears to infer that the rejection is under 35 USC 112, first paragraph. However, the issue under the stated rejection under 35 USC 112, second paragraph is that does the claim as a whole particularly and reasonably point out and distinctly claim the subject matter which applicant regards as the invention. In the absence of a defined definition of the "substantially" from the as-filed specification, the term is at best relative in meanings and therefore does not particularly point out as to what are the metes and bounds of the term or a standard to ascertain applicant's intended scope of the claim. Applicant's argument as to "routine procedure" is not applicable under the stated rejection under 35 USC 112, second paragraph but rather under 35 USC 112, first paragraph, which argument has been addressed by the examiner in the preceding paragraphs with respect to applicant's response to the stated rejection under 35 USC 112, first paragraph.

In addition, the "primitive" is indefinite because it is not apparent as to what is exactly the metes and bounds of the "primitive". What are exactly the types of hematopoietic cells that fall within the scope of "primitive hematopoietic cells"?

In response to applicant's assertion (page 10) that the term "primitive" is well known in the art as hematopoietic cells that are in a less developed stated, applicant's comments are not found persuasive because the assertion is simply an opinion without any factual evidence. Applicants are invited to provide prior art references or factual evidence to indicate that the term is an art recognized term in the art so as to obviate the stated rejection.

Claims 23, 33, 41, 49, 55, 60 and 65 are indefinite in the recitation of "low density" because "low" is relative in meanings and does not identify applicant's intended scope of the claims.

Claim 47 is objected because "rcombinant" should be typed as -- recombinant --.

Applicant asserted that pending claim 47 **as filed** does not recite "rcombinant". However, the examiner maintains that claim 47 in the actual amendment August 18, 2001 does recite "rcombinant".

The entire claim 47 in its exact recitation is reproduced as follows:

47. The cellular grafting method of claim 44 wherein said polypeptide is a rcombinant polypeptide.

***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. ' 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Application's action in amending the specification so as to claim the priority of the as-filed to the filing date of US Pat No. 5,686,278 necessitates the following prior art rejection.

Claims 26, 29 and 87 are rejected under 35 U.S.C. 102(b) as being anticipated by Haberman (US Pat No. 5,354,686).

Haberman teaches a cellular population comprising activated lymphocytes in the presence of at least one extracellular matrix protein including fibronectin in a culture medium is also disclosed on columns 19-22.

Absent evidence to the contrary, the transfection method of Haberman has all of the properties cited in the claims.

Claim 26, 29 and 87 are rejected under 35 USC 102(e) as being anticipated by Ponting (US Pat No. 5,405,772).

Ponting teaches a cellular population comprising viable bone marrow cells which contain hematopoietic cells in a culture medium containing mouse fibronectin proteins available in the prior art (Sigma), column 19.

***Claim Rejections - 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. ' 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 26-31 and 87-90 are rejected under 35 USC 103(a) as being unpatentable over Ponting or Haberman, each of which taken with application admission over the prior art of record on pages 16 and 23

of the as-filed specification.

The rejection of the base claims 26 and 87 are applied here as indicated above. To the extent that Ponting does not teach the use of known functional fibronectin fragments available in the prior art, pages 16 and 23 of the as-filed specification teaches that functionally active fibronectin fragments including H-296 and CH-296 are available in the prior art of record.

It would have been obvious for one of ordinary skill in the art to have employed any fibronectin fragments known in the prior art as long as the fragments are functional fibronectin in the ECM as obvious and minor modifications. One of ordinary skill in the art would have been motivated to have employed fibronectin fragments including the FN-30/35, H-296 and CH-296 in the culture medium of Ponting so as to increase the number of adherent hematopoietic cells in the culture medium or in a culture medium and in the presence of a fibronectin coated solid surface of Haberman so as to support T cell growth and viability.

Thus, the claimed invention as a whole was *prima facie* obvious.

Applicant's assert on page 11 of the response with respect to Haberman is moot in view of the new ground of rejection.

Claims 11-14, 16, 23-39, 44, 45, 47-50, 52-53, 56-58, 62, 63, 67-69 and 79-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim *et al.,* PNAS, Vol. 86, pp. 8892-8896, 1989, taken with any of Williams and Patel (US Pat No. 5,686,278 which has distinct inventive entity that constitutes as prior art under 35 USC 102(e)), and further in view of applicant's admission over the prior art of record on pages 16 and 23 of the as-filed application.

Lim *et al.* teach a method of grafting murine stem cells enriched in hematopoietic stem cells transduced by a replication defective retroviral vector expressing a human ADA gene for long-term expression of the ADA gene in mice transplanted with the cells (entire disclosure). Culture medium

containing the transfected stem cells is also disclosed in the Lim *et al.* reference.

Lim *et al.* do not teach the concept of employing functionally active fibronectin, *e.g.,* FN 30/35 which contain both the binding domains as recited in the claims, to facilitate or enhance the transduction of retrovirus vectors into the cells.

However, at the time the invention was made, Williams and Patel teach a method of obtaining retrovirus transduced blood stem cells comprising infecting the cells with a supernatant containing retrovirus vectors expressing a transgene on FN 30/35 coated dishes so as to enhance the infection efficiency (entire document). The Williams and Patel reference as a whole clearly teaches that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing the retrovirus infecting the stem cells, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

In addition, pages 16 and 23 of the as-filed specification teaches that functionally active fibronectin fragments including H-296 and CH-296 are available in the prior art of record.

It would have been obvious for one of ordinary skill in the art to have employed any fibronectin fragments known in the prior art as long as the fragments contains the essential domains of the FN-30/35 in the grafting method and/or cultures and/or compositions of Lim *et al.* One of ordinary skill in the art would have been motivated to have employed fibronectin fragments including the FN-30/35, H-296 and CH-296 in the grafting methods and/or compositions of Lim *et al.* so as to increase the retroviral transduction into the stem cells, as taught by the Williams and Patel reference.

In addition, it would also have been obvious for one of ordinary skill in the art to not employ a co-cultivation step or retroviral producer cells because the Williams and Patel reference as a whole clearly teaches that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing a supernatant containing the retrovirus expressing a transgene and stem cells desired for retroviral transduction, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 are rejected under 35 U.S.C. 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a), as being unpatentable over Williams *et al.* (US Pat No. 5,686,278 which has distinct inventive entity (William and Patel) that constitutes as prior art under 35 USC 102(e)).

Williams *et al.* teach a method of obtaining retrovirus transduced blood stem cells including human stem cells or cord blood cells deficient in ADA comprising infecting the cells with a supernatant containing retrovirus vectors expressing a transgene, *e.g.,* ADA, on FN 30/35 coated dishes so as to enhance the infection efficiency (entire documents, especially columns 7-12 of Williams *et al.*). The Williams *et al.* reference as a whole clearly teach that as long as functionally active fibronectin including FN 30/35 coated plates were employed for culturing the retrovirus infecting the stem cells, transfection efficiency will be generated as a result of the use of fibronectins during the culturing and infection process.

Absent evidence to the contrary, the methods, cultures and compositions of the reference have all of the properties cited in the claims, or at least, in the alternative, would have been obvious over the methods and compositions as claimed.

Applicant assert on pages 11 and 12 that since applicant now claims priority to filing date of the '278 patent, the '278 would not constitute as a prior art under 35 USC 102(e) or 103(a). However, given that the inventive entity is not the same between the '278 patent and that of the as-filed application, the '278 remains a proper prior art (as "another") under 35 USC 102(e) and 35 USC 103(a).

***Double Patenting Rejection***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,686,278 or claims 1-14 of US Pat No. 6.033.907.

Although the conflicting claims are not identical, they are not patentably distinct from each other because all three sets of claims are readable on

A method for obtaining a transduced population of viable mammalian cells by a retrovirus expressing ADA, a composition containing the transduced populations, and a method of enhancing the transduction of retrovirus vectors into hematopoietic cells, wherein all of the methods and compositions require the presence of substantially pure fibronectin, substantially pure fibronectin fragments, or a mixture thereof, so as to increase the frequency of transduction of the hematopoietic cells by the retrovirus vector.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Kimberly Davis, whose telephone number is **(703) 305-3015**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Clark*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1633

DAVE T. NGUYEN
PRIMARY EXAMINER